

REMARKS

Entry of the foregoing and further and favorable consideration of the subject application are respectfully requested.

As correctly stated in the Official Action, Claims 1-13 and 15-20 are pending in the present application. Claims 1-13 and 15-20 stand rejected.

By the present amendment, Claim 1 has been amended to delete the recitation "general," as suggested by the Examiner in the Official Action (Paper No. 12) on page 4. No new matter has been added.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claim 15 stands rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled. The Examiner argues that the diseases listed in claim 15 are unrelated and could not be addressed by a single pharmaceutical and that agonist/antagonist ability does not give an indication of the pharmaceutical properties of the compound. This rejection is respectfully traversed.

The standard for enablement under 35 U.S.C. § 112, first paragraph, is merely that "one reasonably skilled in the art could make or use the invention from the disclosure in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 U.S.P.Q.2d 1217, 1223 (Fed. Cir. 1988). The skilled artisan can readily use the presently claimed invention based on the disclosure of the specification and the level of knowledge of the art.

The compounds of the present invention act as either agonists or antagonists of RXR receptors (specification page 13, lines 17-19). The specification further provides for methods of determining whether a particular compound of the present invention is either an agonist or antagonist by using either methods known in the art (see page 13, lines 20-24) or by following the methods delineated in the specification on page 13, line 25, to page 15, line 7.

Contrary to the Examiner's statement, the disorders of Claim 15 *are* related. These disorders are all associated with abnormalities of differentiation or proliferation (page 15, line 14, to page 17, line 22, particularly those of the skin, which are well-known in the art to be regulated by RXR receptor stimulation or inhibition. Applicants submit for the Examiner's information a copy of a review article entitled "Therapeutic Applications for Ligands of Retinoic Receptors" (Exhibit 1 - *Current Pharmaceutical Design* 6:25-58 (2000)). Although this article was published after the priority date of the present application, most of the articles summarized therein, which demonstrate the state of the art, predate the present application. The Examiner's attention is directed particularly to Section 4 of the article ("Retinoid Therapeutics: Indications, Mechanisms, and Future Uses") which discusses the use of retinoids in such fields as vitamin A supplementation, skin pharmacology, cancer therapy, emphysema and bronchopulmonary dysplasia of newborns, vascular pharmacology, and diabetes and metabolic disease. Thus, the level of understanding and skill in this art is both high and broad. Based on that well-known in the art and the guidance of the specification, a skilled artisan interested in treating a particular disorder can readily select an appropriate compound, either an agonist or antagonist, for the

particular disease. For instance, if it is known that the progression of a disorder or the pathophysiology underlying the disorder is inhibited by RXR stimulation, the skilled artisan may then select an RXR agonist of the present invention to treat the disorder. There is no inherently complicated or undue experimentation associated with this process.

Accordingly, present Claim 15 meets the requirements of 35 U.S.C. § 112, first paragraph. Withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-13 and 15-20 stand rejected under 35 U.S.C. § 112, second paragraph, as purportedly indefinite in the recitation of a "general" formula.

Without conceding to the merits of this rejection and solely in an effort to expedite prosecution, the recitation "general" has been deleted from independent Claim 1, thereby mooted the rejection. Applicants have not noted any other occurrences of "general" in the remaining dependent claims. Withdrawal of this rejection is respectfully requested.

Conclusions

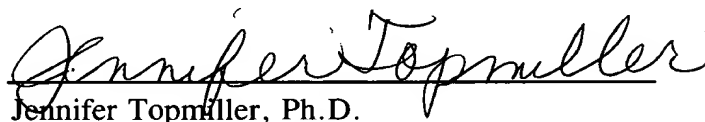
From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

Respectfully submitted,

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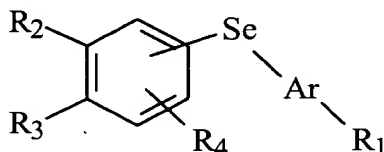
Date: June 26, 2002



Attachment to REPLY & AMENDMENT dated June 26, 2002

Marked-up Claim 1

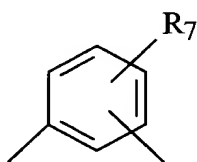
1. (Three Times Amended) A compound having [the general] formula
 (I) below:



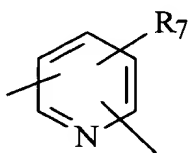
(I)

in which:

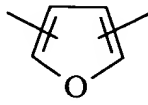
- R_1 represents:
 - (i) a $-CH_3$ radical,
 - (ii) a radical $-CH_2-O-R_5$,
 - (iii) a radical $-COR_6$, R_5 and R_6 having the meanings given below,
- Ar represents a radical selected from the group of radicals of formulae (a) - (e) below:



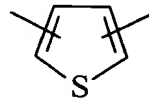
(a)



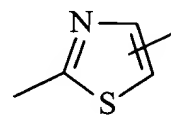
(b)



(c)



(d)



(e)

- R_7 having the meaning given below
- R_2 and R_3 , which may be identical or different, independently represent a radical selected from the group consisting of:
 - (i) a hydrogen atom,
 - (ii) a radical selected from tert-butyl, 1-methylcyclohexyl and 1-adamantyl radicals,
 - (iii) a radical $-OR_8$, R_8 having the meaning given below, and
 - (iv) a polyether radical, it being understood that at least one of the radicals R_2 or R_3 represents a radical (ii),
- R_2 and R_3 taken together can form, with the adjacent aromatic ring, a 5- or 6-membered saturated ring optionally substituted with methyl groups and/or optionally interrupted with an oxygen or sulphur atom,
- R_4 represents a hydrogen atom, a halogen atom, a lower alkyl radical, a radical OR_9 , a polyether radical or a radical COR_{10} ,
 R_9 and R_{10} having the meanings given below,
- R_5 represents a hydrogen atom, a lower alkyl radical or a radical COR_{11} ,

Attachment to REPLY & AMENDMENT dated June 26, 2002

Marked-up Claim 1

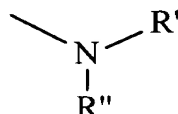
R₁₁ having the meaning given below,

- R₆ represents a radical selected from the group consisting of:

- (i) a hydrogen atom,
- (ii) a lower alkyl radical,
- (iii) a radical OR₁₂,

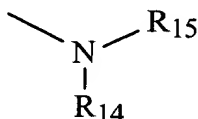
R₁₂ having the meaning given below, and

- (iv) a radical of formula



R' and R'' having the meanings given below,

- R₇ represents a hydrogen atom, a halogen atom, a lower alkyl radical, a nitro radical, a radical OR₁₃, a polyether radical or a radical of the following formula:



R₁₃, R₁₄ and R₁₅ having the meanings given below,

- R₈ represents a hydrogen atom, a lower alkyl radical, an optionally substituted aryl radical, an optionally substituted aralkyl radical, a monohydroxyalkyl or polyhydroxyalkyl radical or a lower acyl radical,
- R₉ represents a hydrogen atom, a lower alkyl radical, an optionally substituted aryl radical, an optionally substituted aralkyl radical, a monohydroxyalkyl or polyhydroxyalkyl radical, a lower acyl radical, a radical $-(CH_2)_n-COOR_{16}$ or a radical $-(CH_2)_n-X$,
n, R₁₆ and X having the meanings given below,
- R₁₀ and R₁₁, which may be identical or different, represent a lower alkyl radical,
- R₁₂ represents a hydrogen atom, a lower alkyl radical, an optionally substituted aryl or aralkyl radical, a monohydroxyalkyl radical or a polyhydroxyalkyl radical,
- R' and R'', which may be identical or different, represent a hydrogen atom, a lower alkyl radical, an optionally substituted aryl radical or an amino acid residue, or alternatively R' and R'' taken together can form, with the nitrogen atom, a heterocycle,
- R₁₃ represents a hydrogen atom or a lower alkyl radical,
- R₁₄ and R₁₅, which may be identical or different, represent a hydrogen atom or a lower alkyl radical,
- R₁₆ represents a hydrogen atom or a lower alkyl radical,
- n represents an integer between 1 and 12 inclusive,

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Marked-up Claim 1

- X represents a halogen atom, and the optical and geometrical isomers of the said compounds of formula (I), as well as the salts thereof.